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Title: Topical Treatments for Chronic Plaque Psoriasis

Article Type: From the Cochrane Library

Keywords: Psoriasis; Review; Drug Administration, Topical; Treatment  
Outcome; Drug Safety

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#### Abstract: Background

Chronic plaque psoriasis is the most common type of psoriasis and is characterised by redness, thickness and scaling. First line management is with topical treatments.

#### Objective

To undertake a Cochrane review of topical treatments for chronic plaque psoriasis

#### Methods

We systematically searched major databases for randomized controlled trials. Trials reported improvement using a range of related measures; standardised, pooled findings were translated onto a 6-point improvement scale.

#### Results

The review included 177 randomised controlled trials with 34,808 participants, including 26 trials of scalp psoriasis and six trials of inverse and/or facial psoriasis. Typical trial duration was 3-8 weeks. When compared to placebo (emollient base), the average improvement for vitamin D analogues and potent corticosteroids was approximately 1 point, dithranol 1.2 points, very potent corticosteroids 1.8 points and combined vitamin D analogue plus steroid 1.4 points once-daily and 2.2 points twice-daily. However, these are indicative benefits drawn from heterogeneous trial findings. Corticosteroids were more effective than vitamin D for treating psoriasis of the scalp. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause skin irritation.

#### Limitations

Reporting of benefits, adverse effects, and safety assessment methods was often inadequate. In many comparisons, heterogeneity made the size of treatment benefit uncertain.

#### Conclusions

Corticosteroids are as effective as vitamin D analogues and cause less skin irritation. However, further research is needed to inform long-term maintenance treatment and provide appropriate safety data.

Title: Topical Treatments for Chronic Plaque psoriasis

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Disclaimer: The results of a Cochrane review can be interpreted differently, depending on people's perspectives and circumstances. The conclusions presented are the opinions of review authors, and are not necessarily shared by The Cochrane Collaboration.

**Capsule summary**

- Chronic plaque psoriasis is the most common type of psoriasis and is characterised by redness, thickness and scaling. First line management is with topical treatments
- On a six-point improvement scale, topical therapies provide an additional benefit over placebo (emollient) of between 1.0 and 2.2 points. Corticosteroids are as effective as vitamin D analogues and cause less skin irritation
- We need more research to inform long-term maintenance treatment and provide appropriate safety data.

## **Abstract**

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Chronic plaque psoriasis is the most common type of psoriasis and is characterised by redness, thickness and scaling. First line management is with topical treatments.

### *Objective*

To undertake a Cochrane review of topical treatments for chronic plaque psoriasis

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We systematically searched major databases for randomized controlled trials. ~~One author extracted study data and assessed study quality. A second author checked these data.~~ Trials reported improvement using a range of related measures; standardised, pooled findings were translated onto a 6-point improvement scale.

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The review included 177 randomised controlled trials with 34,808 participants, including 26 trials of scalp psoriasis and six trials of inverse and/or facial psoriasis. Typical trial duration was 3-8 weeks. When compared to placebo (emollient base), the average improvement for vitamin D analogues and potent corticosteroids was approximately 1 point, dithranol 1.2 points, very potent corticosteroids 1.8 points and combined vitamin D analogue plus steroid 1.4 points once-daily and 2.2 points twice-daily. However, these are indicative benefits drawn from heterogeneous trial findings. Corticosteroids were more effective than vitamin D for treating psoriasis of the scalp. For both body and scalp psoriasis, potent corticosteroids were less likely than vitamin D to cause skin irritation.

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25 Corticosteroids are as effective as vitamin D analogues and cause less skin irritation. However,  
26 further research is needed to inform long-term maintenance treatment and provide appropriate  
27 safety data.

28

29 Key words: Psoriasis; Review; Drug Administration, Topical; Treatment Outcome; Drug Safety

30

31

## 32    **Abbreviations**

33    CI: confidence interval

34    IAGI: Investigator's assessment of global improvement

35    NSAID: non-steroidal anti-inflammatory drug

36    RD: risk difference

37    SMD: standardised mean difference

38    TNF $\alpha$ : tumour necrosis factor alpha

39    VDR: vitamin D receptor

40    VDRE: vitamin D responsive element

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42

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## Background

Psoriasis is a chronic inflammatory skin disease with a prevalence ranging from between 1 and 2% in the UK and northern European populations<sup>1,2</sup> to 0.1 to 0.3% in the Far East<sup>3</sup> and China.<sup>4</sup> Chronic plaque psoriasis accounts for 90% of psoriasis cases,<sup>5</sup> and most commonly affects the knees, elbows, lower back and scalp. It is characterised by red patches of thickened skin (plaques) covered in silver scales. There is a wide spectrum of disease severity from single plaque to more than 90% of the skin surface. Psoriasis can lead to social isolation,<sup>6</sup> stigmatisation<sup>7</sup> and adversely affect the quality of daily life.<sup>8-15</sup>

~~The way that psoriasis develops is complicated and appears to be influenced by many factors including genetic changes, local trauma, infections, certain drugs (e.g. beta-blockers), endocrine factors, sunlight, alcohol, smoking and stress.<sup>16</sup> Psoriasis skin lesions are characterised by epidermal hyperproliferation, abnormal keratinocyte differentiation and a lymphocyte inflammatory infiltrate.<sup>17-19</sup> Psoriasis is recognised as an immune-mediated disorder, with tumour necrosis factor alpha (TNFα), dendritic cells and T-cells all contributing to its pathogenesis.<sup>20</sup> A meta-analysis of three genome-wide association studies (GWAS) has identified 15 new susceptibility loci for psoriasis,<sup>21</sup> bringing the total number of loci associated with psoriasis to 36.~~

Topical treatments include most prominently vitamin D analogues and topical corticosteroids but also tar-based preparations, dithranol, salicylic acid and topical retinoids.<sup>16</sup> As there is no strong evidence-base on which to consistently sequence topical treatments,<sup>17</sup> treatment should be tailored to individual need.<sup>18,19</sup> Emollients are generally used in addition to topical treatments, to normalise hyperproliferation, differentiation, and to exert anti-inflammatory effects.<sup>20</sup>

This paper is based on a Cochrane review most recently substantially amended in The Cochrane Library 2013, Issue (~~to follow~~3) (see <http://www.thecochranelibrary.com>).<sup>21</sup> Cochrane reviews are



regularly updated as new evidence emerges and in response to feedback, and The Cochrane Library should be consulted for the most recent version of the review.

## **Objective**

To compare the effectiveness, tolerability and safety of topical treatments for chronic plaque psoriasis, relative to placebo; to compare vitamin D analogues with other topical treatments.

## **Methods**

### Inclusion criteria

We included randomised controlled trials in the review. Trials could be either placebo-controlled or head-to-head with a vitamin D preparation (head-to-head trials compare active treatments with each other). Trials of systemic or ultra-violet (phototherapy) treatments with adjunctive topical treatment were not eligible for inclusion. For within-patient studies, we included only those studies that clearly adopted a left-right design and excluded studies where multiple plaques are treated with more than two products. If no ~~useful~~useable effectiveness, withdrawal or adverse events data were available, either from the published paper or from sponsors or triallists, we excluded the study.

### Data extraction

One author extracted study data and assessed study quality. A second author checked these data.

### Searches

Table 1 shows the electronic databases searched. Ongoing studies were identified from the UK Clinical Research Network Study Portfolio and the metaRegister of Current Controlled Trials. We routinely contacted triallists and companies for missing data.

TABLE 1 HERE

### Outcomes

We extracted data from trials on the four primary outcomes (Table 2). Trials often reported more than one measure, but no measure was reported by all trials. We therefore devised a 'combined endpoint', ~~which to~~ facilitated treatment comparisons. Our review summary focused on this measure. We constructed the combined endpoint by taking primary outcomes data in the following order listed in Table 2, according to availability: investigator global assessment; total severity score; PASI; patient global assessment (see Table 2 for definitions). We analysed findings in RevMan 5.2<sup>22</sup> using a standardised mean difference (SMD) statistic in a random effects model. The SMD is the difference between the means (value for the intervention group less value for the comparator group), divided by the pooled standard deviation. The SMD is therefore 'unit-neutral', i.e. independent of the scale used for measurement. This approach is therefore valid for the comparison of different outcome measures, provided that they are all essentially assessing the same characteristics: redness, thickness and scaling. An alternative approach is to use binary outcomes such as success rates, but this approach imposes an additional assumption that the cut-off for 'success' is constant across outcomes; dichotomisation of continuous scales is also an inefficient use of information. Where studies did not report estimates of variance, we derived them from confidence intervals or from P values where possible, or imputed them deterministically by pooling the standard deviations of treatment cohorts fully reported in trials and adjusted for scale. These pooled statistics were used to translate the combined endpoint back to natural units on a 6-point investigator's improvement scale (see Table 2). For example, if an average patient achieves a 'mild' improvement with placebo, but a 'moderate' (or 'marked') improvement with the active treatment, this is equivalent to a one point (two point) improvement.

We extracted data on five secondary outcomes: data on withdrawal due to any cause, to adverse events and to treatment failure, as well as a count of individuals experiencing adverse events due to local (cutaneous) and systemic effects (e.g. hypercalcaemia). As definitions of withdrawal and adverse events vary between trials, data were summarised using a random effects risk difference

(RD) metric. Heterogeneity (inconsistency between studies) was assessed using the I-squared statistic, which is the percentage of the variability in effect estimates from the different subgroups in a meta analysis that is due to genuine subgroup differences rather than sampling error (chance).<sup>23</sup>

TABLE 2 HERE

### Structure of the review

The Cochrane review grouped data into 19 comparisons. These cover placebo-controlled trials of the body (comparisons 1-6); head-to-head trials of the body (comparisons 7-15); trials of inverse psoriasis (psoriasis affecting the folds of the skin) or facial psoriasis (comparisons 16 and 17); and trials of scalp psoriasis (comparisons 18 and 19).

## Results

The review included 177 randomised controlled trials, including 26 trials of scalp psoriasis and six trials of inverse and/or facial psoriasis. The oldest trial was published in 1975 and the most recent in 2011.

There were 106 placebo controlled trials, 84 compared treatments directly (head-to-head), with 13 trials reporting both placebo-controlled and active comparisons. The trials included 34,808 participants, with a mean age of 47 (range: 2 to 97) and a higher proportion of men (57%). Treatment duration was 7 weeks on average, but this ranged from one week to 52 weeks. As a marker of study quality, 74% of the trials were double-blind. Single-blind (investigator only) and 'open' (no blinding) trials were typically those in which it was impossible to conceal the identity of investigated products from patients (e.g. coal tar, dithranol, or products using different vehicle formulations such as cream vs. ointment). Forty-seven trials (27%) clearly reported the randomisation method, and concealment of treatment allocation was considered 'adequate' in 15 trials (9%).

### Placebo-controlled trials of body psoriasis (comparisons 1-6)

Most treatments for psoriasis of the body were more effective than placebo. The pooled effect (SMD) across all vitamin D analogues was -0.90 (95% CI -1.06 to -0.72; 30 studies; 4986 patients;  $I^2$ : 87.5%), equivalent to 1.0 on a 6-point improvement (IAGI) scale. The average effect was similar for calcipotriol, calcitriol and tacalcitol while findings for other agents were limited to single trial reports. However, there was significant variation in findings of individual trials ranging from 0.1 to 3.6 (an outlier) on a 6-point IAGI scale.

FIGURE 1 HERE

Potent topical corticosteroids were similarly effective: in 13 trials with 2216 patients, the pooled effect across all studies was -0.89 (95% CI -1.06 to -0.72;  $I^2$ : 65.1%), equivalent to 1.0 on a 6-point IAGI scale. However betamethasone dipropionate BD was significantly more effective than betamethasone dipropionate OD (1.6 vs. 0.9 on a 6-point IAGI scale). Only betamethasone dipropionate OD and BD, betamethasone valerate and fluticasone propionate provided evidence from more than one placebo-controlled trial.

FIGURE 2 HERE

The pooled effect across 10 trials (1264 patients) of very potent steroids was -1.56 (95% CI -1.87 to -1.26;  $I^2$ : 81.7%), equivalent to 1.8 on a 6-point IAGI scale. Overall findings were similar for clobetasol propionate and halobetasol, the only two agents studied, although there was significant variation between individual trial findings ranging from 1.0 to 2.8 on a 6-point IAGI scale.

FIGURE 3 HERE

Of the three placebo-controlled trials of dithranol (covering 47 patients in total), the most recent was published in 1997. The SMD for the combined endpoint was -1.06 (95% CI -1.66 to -0.46;  $I^2$ : 37%), equivalent to 1.2 on a 6-point IAGI scale. There was variation in treatment regimens between the trials and the effect in individual trials ranged from 0.8 to 1.9 on a 6-point IAGI scale.

FIGURE 4 HERE

Combination treatment (vitamin D plus a corticosteroid) was compared with placebo in five trials. The SMD for the combined endpoint was -1.44 (95% CI -1.76 to -1.12;  $I^2$ : 93%), although twice-daily combination treatment (SMD -1.90; 95% CI -2.09 to -1.71) suggested a larger effect than once-daily

treatment (SMD -1.21; 95% CI -1.50 to -0.91). On a six-point IAGI scale, these equate to improvements of 2.2 and 1.4 points respectively.

We also reviewed 26 treatments that did not fit the above categories, including tazarotene (one trial) which improved psoriasis by one point more than placebo on a six-point IAGI scale, a similar effect to vitamin D analogues and potent corticosteroids.

### **Head-to-head trials of body psoriasis (comparisons 7-15)**

Direct (head-to-head) comparisons were made of vitamin D analogues (alone or in combination) with other treatments. Fourteen trials compared vitamin D analogues directly with potent corticosteroids (3542 patients). Although there was no significant difference between the two groups of drug, substantial heterogeneity underlay this finding. Over 80% of patients were recruited into seven trials. Three trials comparing calcipotriol with betamethasone dipropionate found the steroid to be more effective (SMD 0.43; 95% CI 0.28 to 0.58,  $I^2=50\%$ ) or 0.5 points on a six-point IAGI scale, while four trials comparing calcipotriol with betamethasone valerate found no difference (SMD -0.12; 95% CI -0.26 to 0.02,  $I^2=42\%$ ).

The comparison of vitamin D against very potent steroids found no significant difference between calcipotriol and clobetasol propionate (SMD -0.06; 95% CI -0.57 to 0.44,  $I^2=26\%$ ), a finding based on two small trials and only 82 patients.

Combination therapy (vitamin D plus corticosteroid) was more effective than either individual product used as monotherapy. Most information related to calcipotriol and betamethasone dipropionate including 76% of patients. Calcipotriol combined with betamethasone dipropionate was more effective than calcipotriol alone (SMD -0.57 95%CI: -0.42, -0.72,  $I^2=81\%$ ), and calcipotriol combined with betamethasone dipropionate was more effective than betamethasone dipropionate

alone (SMD -0.40 95%CI: -0.52, -0.27,  $I^2=42\%$ ). These changes equate to approximately 0.6 and 0.4 points respectively on a six-point IAGI scale.

Findings on the comparison of dithranol against vitamin D were highly heterogeneous ( $I^2=95\%$ ), possibly reflecting variation in the dithranol regimens employed by trials and in the baseline severity of trial participants.

### **Trials of inverse or facial psoriasis (comparisons 16-17)**

There were 2 small placebo-controlled trials of three agents and only 122 patients in total. These provided tentative evidence in favour of betamethasone valerate, calcipotriol and the topical calcineurin inhibitor pimecrolimus (by 3.25, 1.2 and 1.0 points on a six-point scale). There were four head-to-head trials (588 patients) involving vitamin D analogues each comparing different agents. Of these 408 (70%) of patients were recruited to one trial comparing calcipotriol and hydrocortisone with calcipotriol: combination treatment was more effective (SMD -0.30 95%CI: -0.11 to -0.50).

### **Trials of scalp psoriasis (comparisons 18-19)**

We identified 14 placebo-controlled trials in scalp psoriasis involving 3011 patients. Most evidence concerned four comparisons. Calcipotriol (SMD -0.72, 95%CI: -1.28 to -0.16,  $I^2=69\%$ ) delivered 0.9 points improvement; betamethasone dipropionate (SMD: -1.09, 95%CI: -1.29 to -0.90,  $I^2=0\%$ ) delivered 1.3 points improvement; clobetasol propionate (SMD -1.57, 95%CI: -1.81 to -1.34;  $I^2=43.3\%$ ) delivered 1.9 points; while calcipotriol and betamethasone dipropionate combined ( $I^2=90\%$ ) varied from 0.7 to 1.5 points, possibly reflecting the ethnically different patient populations.<sup>24 25</sup>

In 5 head-to-head trials (2337 patients), vitamin D was consistently less effective than potent or very potent corticosteroids (SMD: 0.45, 95%CI: 0.36 to 0.53,  $I^2=1\%$ ) equating to 0.6 points on a six-point IAGI scale. Monotherapy with vitamin D was consistently less effective than vitamin D combined

with potent corticosteroids (4 trials, 2581 patients) although findings were heterogeneous ( $I^2=82\%$ ) ranging between 0.5 and 1.2 points on a six-point IAGI scale. Combination therapy was more effective than potent steroids alone (SMD: -0.18, 95%CI: -0.26 to -0.10,  $I^2=0\%$ ) equating to 0.2 points. There was no overall significant difference between calcipotriol and coal tar polytherapy although findings were heterogeneous (3 trials, 835 patients,  $I^2=90\%$ ).

## **Adverse events**

We summarised data on the rate of systemic adverse events (those occurring within the body) and the rate of local (cutaneous) adverse events such as skin irritation. Of the vitamin D analogues, most data were available for calcipotriol. Used on the body, calcipotriol monotherapy was associated with a significantly higher rate of local adverse events than potent steroids ( $I^2=80\%$ , range of the individual studies from 6% to 22%) or combination therapy of calcipotriol plus steroid (RD 6%, 95%CI: 4% to 8%,  $I^2=9\%$ ).

Similarly, used on the scalp, calcipotriol monotherapy was associated with a significantly higher rate of local adverse events than steroids ( $I^2=78\%$ , range from 7% to 24%) or combination therapy of calcipotriol plus potent steroid (RD 9%, 95%CI: 6% to 12%,  $I^2=28\%$ ). However, when used on the body calcipotriol was associated with a significantly lower rate of local adverse events than dithranol (RD -25%, 95%CI: -32% to -17%,  $I^2=51\%$ ). Comparative data for other agents was limited. No trial found a significant difference in the rate of systemic adverse events.

## **Conclusions**

Evidence from large numbers of trials indicates that most topical treatments alleviate the symptoms of psoriasis. While trial evidence is considerable for vitamin D analogues and steroids alone or in combination and for dithranol, the evidence for a large number of other agents is inadequate and often limited to single small trials. There is also an increasing evidence base for long-term



257 maintenance regimes which vary in frequency and dose and so are difficult to summarise. Details of  
258 these maintenance regimes and less-researched regimes are reported in the Cochrane review.

259  
260 On average, when compared to placebo (emollient base) vitamin D analogues and potent steroids  
261 may achieve an approximate 1 point gain on a 6 point improvement scale, dithranol 1.2 points, very  
262 potent corticosteroids 1.8 points, and combined vitamin D analogue plus steroid 1.4 points once-  
263 daily and 2.2 points twice daily. However these indicative benefits should be viewed with caution as  
264 they are drawn from heterogeneous trial findings.

265  
266 Although vitamin D analogues and corticosteroids are equally effective for treating psoriasis of the  
267 body, corticosteroids appear to be more effective than vitamin D for treating psoriasis of the scalp.  
268 Combined treatment of vitamin D with corticosteroid appears to have a small additional benefit  
269 above vitamin D alone or corticosteroid treatment alone.

270  
271 The reporting of trials prohibited adequate exploration of the potential causes of heterogeneity. For  
272 example, treatment performance may be affected by disease severity, though poor reporting of  
273 baseline severity in trials meant this could not be confirmed. Adherence may also be enhanced  
274 when using a combined product, if application time is shorter.

275  
276 Potent corticosteroids are less likely than vitamin D to cause local adverse events. Our review found  
277 no difference between placebo and any topical treatment in the assessment of systemic adverse  
278 events. However, this may reflect an absence of evidence (trials failing to appropriately assess these  
279 events over adequate time periods) rather than being evidence of absence.

280  
281 Although current evidence demonstrates that topical steroids are as effective as and at least as well  
282 tolerated as vitamin D analogues, concern remains about the potential safety problems associated

283 with corticosteroids.<sup>26</sup> Concerns include the risk of rebound (a worsening of disease following  
284 treatment discontinuation), skin atrophy (skin thinning) and tachyphylaxis (decreasing response to  
285 the drug) after long-term use.<sup>27</sup> Methods to assess rebound have been developed and should be  
286 used in future research.<sup>28</sup> Regarding skin thinning, one problem with psoriasis is that the skin is very  
287 thick and a goal of therapy is to reduce the thickness of lesional (epidermal) skin. The issue may  
288 become a historical one, if newer safer steroids, currently being developed and evaluated for atopic  
289 dermatitis, subsequently demonstrate efficacy and safety in chronic plaque psoriasis.

290

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Electronic databases searched

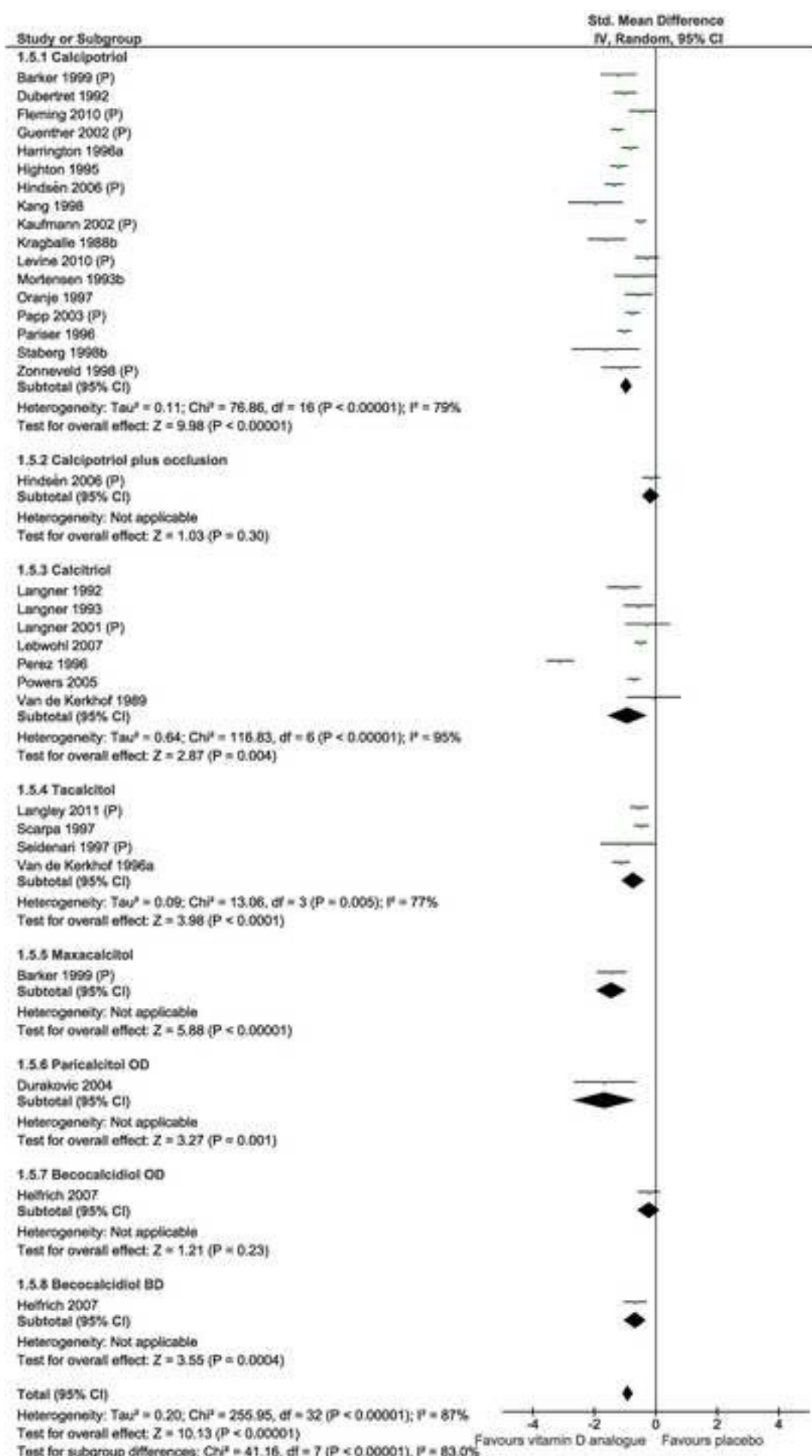
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Database	Date searched
EMBASE	to 2011/02
MEDLINE	to 2011/02
Science Citation Index (SCI)	to 2011
Conference Proceedings Citation Index (CPCI-S)	to 2011
Biosis	to 2011
Dissertation Abstracts	all publication years
Inside Conferences	all publication years
CENTRAL Cochrane Library web interface	to 2011/02
Cochrane Skin Group's Trials Register	to 2011/02

Rank <sup>1</sup>	Primary Outcome measures	Construct
1	Investigator Assessment of Global Improvement; <sup>2</sup> or the equivalent static score, Investigator Global Assessment of Disease Severity	Improvement from baseline, usually scaled from worse to cleared; higher scores indicate greater improvement. Disease severity usually scaled from ‘absence of disease’ to ‘very severe disease’; higher scores indicate more severe disease.
2	Total Severity Score	Redness (erythema), thickness (infiltration) and scaling (sometimes also itching (pruritis)) of target plaque(s). Scored separately then summed.
3	Psoriasis Area Severity Index (PASI)	Redness, thickness, and scaliness of the lesions (each graded on a 0 to 4 scale), weighted by the area of involvement (0 to 6) and summed. Scored from 0 to 72 (if head excluded: 0 to 68)
4	Patient (or Subject) Assessment of Global Improvement; <sup>2</sup> or the equivalent static score, Patient (or Subject) Global Assessment of Disease Severity	See <i>Investigator Assessment of Global Improvement</i>
	<sup>1</sup> Order for inclusion in ‘combined endpoint’ <sup>2</sup> Global improvement data are entered as a negative values, thus a reduction denotes a positive improvement for the active treatment consistent with other measures.	

# Chronic plaque psoriasis: vitamin D analogues vs. placebo

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# Chronic plaque psoriasis: potent corticosteroids vs. placebo

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